Notes

Quinine: An Inexpensive Chiral Solvating Agent for the Determination of Enantiomeric Composition of Binaphthyl Derivatives and Alkylarylcarbinols by NMR Spectroscopy

Carlo Rosini, Gloria Uccello-Barretta, Dario Pini, Carlo Abete, and Piero Salvadori*

Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56100 Pisa, Italy

Received January 29, 1988

When nuclear magnetic resonance spectroscopy is employed for determining enantiomeric compositions of organic compounds,[1,2] the presence of an external chiral auxiliary is required so that originally enantiotopic nuclei become diastereotopic. The chiral auxiliary can convert the enantiomers of the substrate either to stable[1] diastereoisomeric derivatives (e.g., as does α-(trifluoromethyl)-α-methoxyphenylacetyl chloride, Mosher reagent) or to nonisolable diastereoisomeric solvates,[2] when a chiral solvating agent like 2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's reagent) is employed. Disadvantages of some of the commonly employed chiral auxiliaries are that they are often expensive or, in the case of formation of the stable diastereoisomeric derivatives, chemical manipulations are required which can be tedious and time consuming. Moreover, one must be concerned with the enantiomeric purity of the reagent.[3] Therefore, the development of an easily available and inexpensive optically pure chiral solvating agent (CSA) to be used for NMR evaluation of enantiomeric excesses is a desirable goal.

The complex chemical structure of quinine (a secondary alcoholic group, two basic nitrogen atoms, a heteroaromatic system) makes this molecule capable of interacting with the optical antipodes of many organic compounds and of being of potential utility as a CSA. In fact, it has been already observed[4] that the proton nuclear magnetic resonance spectra of (−)-dihydroquinine and racemic dihydroquinine are clearly different, suggesting that this molecule can generate its own NMR nonequivalence. More recently,[5] this indication found a strong support: diastereoisomeric solvates can be formed by interaction of quinine with binaphthyl derivatives, and the structure of these can be studied by NMR spectroscopy. Therefore, the idea originated of employing such compounds (general formula I, Chart I) for testing the use of quinine as a chiral solvating agent. The investigation was extended to alkylarylcarbinols (general formula II, Chart I), considering that they have been successfully separated[7] in enantiomers by means of a silica-supported quinine chiral stationary phase.

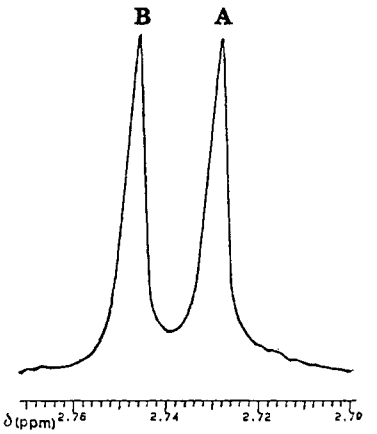


Figure 1. ^{1}H NMR resonances of methyl protons of NHMe groups of adducts (A and B) formed by racemic **8** with quinine (300 MHz, $CDCl_3$).

The substrates we have investigated are the binaphthyl derivatives **1–8** and alkylarylcarbinols **9–14**. ^{1}H and ^{19}F NMR spectra of mixtures of quinine and the above compounds were recorded in $CDCl_3$ at 300 and 282 MHz respectively. The results obtained and the experimental conditions employed are summarized in Table I.

In all cases examined, the signal separations obtained are great enough to allow one to carry out the enantiomeric excess (ee) determinations. In Figure 1 is reported the region of the ^{1}H NMR spectrum of **8**, relative to the resonance of methyl protons of the NHMe groups. Compounds such as binaphthyl monoalkyl ethers (compounds **1**, **2**, and **6**) as well as compounds **3** and **8** are particularly suitable for these measurements because they contain groups that serve as sensitive probes for magnetic unequivalence: the signals stemming from these groups give rise to appreciable separations of signals of (formerly) enantiotopic groups in the presence of quinine. In compounds that are originally devoid of such reporter groups, simple derivatization (e.g., treatment with acyl chloride) may introduce the necessary probe for ee determinations via NMR measurements. Compounds **4**, **5**, and **7** exemplify such derivatives on which it is possible to carry out measurements of enantiomeric purity. For **5**, measurement at lower temperature is necessary to provide adequate signal splitting, which in general increases as temperature is lowered. In general, the ee of binaphthol derivatives which do not contain reporter groups can be determined

(1) Yamaguchi, S. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, p 125.

(2) (a) Weisman, G. R. *Asymmetric Synthesis*; Morrison, J. D., Academic: New York, 1983; Vol. 1, p 153. (b) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 264.

(3) Halterman, R. L.; Roush, W. R.; Hoong, L. K. *J. Org. Chem.* **1987**, *52*, 1152.

(4) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871.

(5) As a part of our investigation on the preparation and the use of *Cinchona* alkaloid based chiral stationary phases for the HPLC resolution of racemates, the interaction of enantiomeric substrates with quinine (considered as a soluble model of the chiral support) has been studied.[6] It has been observed that, at least in the case of the monoisopropyl ether of binaphthol, nonequivalence is induced by quinine in the signals of the CH and CH_3 groups: from the area of these signals, the enantiomeric excess of enriched samples can be easily evaluated.

(6) Salvadori, P.; Rosini, C.; Pini, D.; Bertucci, C.; Altemura, P.; Uccello-Barretta, G.; Raffaelli, A. *Tetrahedron.* **1987**, *43*, 4969.

(7) Pini, D.; Rosini, C.; Bertucci, C.; Altemura, P.; Salvadori, P. *Gazz. Chim. Ital.* **1986**, *116*, 603.

0022-3263/88/1953-4579$01.50/0

Table I. Chemical Shifts[a] of Some NMR Signals of Adducts (A and B) Formed by Racemic 1–8 (General Formula I) and 9–14 (General Formula II) with Quinine[b] ($CDCl_3$, 25 °C)

	X	X′	Y	Y′	R	Ar	resolved signals	A	B	T, °C
1	H	H	OH	OMe			Me	3.69	3.76	25
2	H	H	OH	O*i*Pr			Me	0.80	0.84	25
							Me′	0.94	0.97	25
							CH	4.20	4.28	25
3	OMe	OMe	OH	OH			Me	3.47	3.52	25
4	H	H	OH	OCOMe			Me	1.76	1.77	25
5	H	H	OH	OCO-*t*-Bu			*t*-Bu	0.67	0.69	−50
6	H	H	OH	$OCH_2CH{=}CH_2$			CH_2	4.29	4.43	25
7	H	H	NH_2	NHCOMe			Me	1.80	1.81	25
8	H	H	NHMe	NHMe			Me	2.73	2.75	25
9					Me	Ph	Me	1.38	1.39	25
10					*t*-Bu	*p*-$OMeC_6H_4$	*t*-Bu	0.78	0.80	−50
11					CF_3	9-anthryl	CF_3	15.69[c]	15.76[c]	25
12					Me	2-thienyl	CH	5.05	5.07	25
13					*i*-Pr	1-naphthyl	Me	0.62	0.63	−50
							Me′	0.95	0.97	−50
14					CH_2OH	*m*-MeC_6H_4	Me	2.20	2.22	25

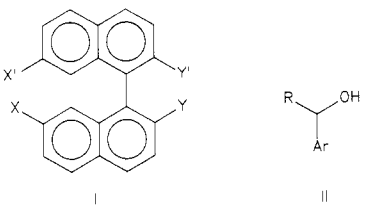
[a] ^1H and ^{19}F NMR chemical shifts are referred to TMS and $CFCl_3$ respectively as internal standards. [b] Experiments have been carried out by mixing 5–10 mg of the sample with a threefold excess of quinine in $CDCl_3$. For compounds 1–8, no significant variations of the chemical shifts of the reporter group were observed in the range of molar ratios from 1:1 up to 1:3. [c] ^{19}F NMR chemical shifts.

simply by converting the compound to the monoacetate and obtaining the NMR spectrum in the presence of quinine.

The enantiomers of simple alkylarylcarbinols such as **9–14** exhibit different chemical shifts when mixed with quinine. The ^{19}F NMR spectrum of a mixture of **11** and quinine shows clear separation of the fluorine signals of each antipode, and the ee of this compound can be easily evaluated.

The above data indicate that quinine can be conveniently used as a CSA for the determination of enantiomeric purities of binaphthyl derivatives and alkylarylcarbinols via NMR, simply by adding to the solution of the antipodes an excess of quinine in a NMR tube. The measurements can be carried out quickly because no chemical reactions have to be carried out. The major advantage of quinine over other commercially available chiral solvating agents can certainly be found in the cost.[8] In principle, a disadvantage of the quinine technique could be the complexity of the quinine NMR spectrum, with possible overlap of signals in the regions of interest (this could be particularly true if a comparison with Pirkle's CSA is made). However, it is important to point out that in all the cases examined no such overlap has been observed, allowing then an easy determination of enantiomeric excesses. It is also noteworthy that binaphthyl derivatives are largely employed as chiral ligands[9] in some efficient enantioselective reactions, while alkylarylcarbinols are often products of asymmetric processes; therefore, an inexpensive and simple method for determining their enantiomeric purity could be extremely useful to the synthetic organic chemist. In addition, these results represent a further use in organic chemistry of quinine, a compound that has been successfully employed as classical resolving agent,[10] chiral auxiliary in both catalytic[11] and stoichiometric asymmetric synthesis,[12] and very recently, in the preparation of chiral stationary phases[6,7] for the liquid chromatographic separation of enantiomers.

Chart I



I II

Experimental Section

Preparation of Compounds. Compounds **9** and **11** were commercial samples from Aldrich and used without further purification. Compounds **1**, **2**, and **6** were prepared by alkylation of binaphthol (Fluka, Buchs, CH) with the suitable alkyl halide following a known procedure[13] while **4** and **5** have been obtained by treatment of binaphthol with acetyl chloride or pivaloyl chloride, respectively, in methylene chloride as solvent. Compound **3** has been obtained by a copper–benzylamine-catalyzed coupling of 2-hydroxy-7-methoxynaphthalene, following Brussee and Jansen.[14] Compounds **7** and **8** were prepared by means of the procedure of Miyano et al.[15] The synthesis of **10** has been described elsewhere.[7] Compound **12** has been prepared by acetylation of thiophene and successive reduction of the ketone with $NaBH_4$. Compound **13** was obtained by addition of *i*-PrMgCl to 1-naphthaldehyde and successive hydrolysis. Compound **14** was prepared by the asymmetric stoichiometric osmylation of *m*-methylstyrene following the procedure described by Sharpless.[16] Elemental analyses and the NMR spectra were consistent with the expected structures.

NMR Measurements. The NMR measurements were performed on a Varian VXR-300 spectrometer operating at 300 MHz for ^1H and 282 MHz for ^{19}F, in $CDCl_3$ as solvent. The temperature was controlled (accuracy ±1 °C) by the Varian control unit.

(8) The prices of commercially available CSA are $1.50/g for quinine, against an average price for lanthanide complexes of $15/g and of approximately $200/g for Pirkle's reagent.

(9) (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. (b) Kabuto, K.; Yoshida, T.; Yamaguchi, S.; Miyano, S.; Hashimoto, H. *J. Org. Chem.* **1985**, *50*, 3013.

(10) (a) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981. (b) Newman, P. *Optical Resolution Procedures for Chemical Compounds*; Optical Resolution Information Center: Manhattan College, Riverdale, New York, 1981.

(11) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.

(12) See, for instance: Cervinka, O.; Belovsky, O. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3897.

(13) Pirkle, W. H.; Schreiner, J. L. *J. Org. Chem.* **1981**, *46*, 4988.

(14) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261.

(15) Miyano, S.; Nawa, M.; Mori, A.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2171.

(16) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

Registry No. 1, 35193-70-5; 2, 79044-24-9; 3, 79044-29-4; 4, 79044-27-2; 5, 114459-67-5; 6, 79044-26-1; 7, 115510-90-2; 8, 93621-64-8; 9, 13323-81-4; 10, 98976-10-4; 11, 60686-64-8; 12, 115510-91-3; 13, 115463-56-4; 14, 115463-57-5; quinine, 130-95-0.

Metal Catalysis in Oxidation by Peroxides.[1] A ^{17}O NMR Spectroscopic Investigation of Neutral and Anionic Molybdenum Peroxo Complexes

V. Conte,* F. Di Furia, and G. Modena

Centro di Studio sui Meccanismi di Reazioni Organiche del CNR, Dipartimento di Chimica Organica dell'Università, via Marzolo 1, 35131, Padova, Italy

O. Bortolini*

Dipartimento di Chimica dell'Università, via Borsari 46, 44100, Ferrara, Italy

Received January 28, 1988

In connection with our interest[2] in the mechanism of metal-catalyzed oxidations[3] of various organic substrates with peroxides and, in particular, in the structure of the peroxo species involved, we have undertaken a ^{17}O NMR investigation of a series of neutral[4] and anionic[1,5] molybdenum (VI)–oxodiperoxo complexes. The broad scope of ^{17}O NMR spectroscopy as a structural probe is well known.[6] As an example, this technique has been successfully applied to the study of polyoxo anions of the early transition elements in solution[6] and quantitative correlations have been established.[6,7] In particular, a chemical shifts scale for molybdenum-bound oxygens has been constructed.[6] More recently, ^{17}O NMR investigations of oxo, peroxo, and superoxo derivatives of V, Cr, Mo, W, Fe, Ir, and Pt have been reported in the literature.[8-10]

Neutral molybdenum–peroxo complexes of the type $MoO(O_2)_2L$ (L = HMPT, DMF, Py, etc.) oxidize nucleophilic substrates such as alkenes or sulfides both in protic and aprotic solvent via an electrophilic peroxo oxygen transfer mechanism,[2,3] whereas they are rather unreactive toward alcohols.

By contrast, anionic molybdenum–peroxo complexes of the type $[MoO(O_2)_2PIC]^-Bu_4N^+$ (PIC = picolinic acid anion) or $[MoO(O_2)_2PICO]^-Bu_4N^+$ (PICO = picolinic acid *N*-oxido anion),[1] soluble in aprotic solvents owing to the presence of the lipophilic cation, readily oxidize primary and secondary alcohols to the corresponding carbonyl compounds.[1,11] At the same time, their efficiency as electrophilic oxidants is greatly reduced, though not cancelled.[12] In particular, the oxidation of very nucleophilic substrates such as sulfides is still feasible.[11,12]

Table I. ^{17}O NMR Chemical Shifts of the Oxo Resonance of Various Oxo-Diperoxo Mo(VI) Complexes

complex	δ (natural)[a]	δ (enriched)	lit.[8]
$MoO(O_2)_2HMPT$	840 (DCE)	846 (DCE)[b]	863[d]
	857 (CH_3CN)	840 (DCE)[c]	
	830 (CH_2Cl_2)	855 (CH_3CN)[c]	
$MoO(O_2)_2PyO$	854 (CH_3CN)	854 (CH_3CN)[c]	
$MoO(O_2)_2Py$		865 (CH_3CN)[c]	897[d]
$[MoO(O_2)_2PIC]^-Bu_4N^+$	844 (DCE)	847 (DCE)[b]	
		849 (CH_3CN)[b]	
		847 (DCE)[c]	
$[MoO(O_2)_2PICO]^-Bu_4N^+$	834 (DCE)	833 (DCE)[b]	
		836 (CH_3CN)[b]	
		834 (DCE)[c]	
		843 (CH_3CN)[c]	
$[MoO(O_2)_2PIC]^-H_3O^+$		840 (CH_3CN)[c]	940[d]

[a] Saturated solution (0.2–0.01 M) of unlabeled peroxo complexes. Signal/noise ≥ 5. [b] Peroxo compounds prepared in H_2O–$H_2{}^{17}O$ (10% enrichment Stohler Isotope Chemicals). [c] Saturated solution of unlabeled peroxo complexes after shaking with minute amounts of $H_2{}^{17}O$. [d] Solvent not specified.

The different oxidation chemistry of neutral and anionic peroxo complexes could be accompanied by some difference in the ground-state structure being the localization of the negative charge of the anions a central point. The formation of a peracid-like, end-on complex, such as Mo–O–O$^-$, in solution is rather unlikely. Several pieces of evidence discussed in previous papers,[2,13-15] and even ^{17}O NMR investigations of the peroxo oxygens,[8,9] militate against this hypothesis. An alternative possibility, i.e. that the negative charge is mainly located on the Mo=O moiety, giving rise to oxo anions like species such as Mo–O$^-$, is, in turn, somehow questioned by the X-ray data available.[1] These, in fact, indicate that in the solid state the Mo–O bond lengths are almost the same either in neutral[16-18] or in anionic species.[1,5] Indeed the same pentagonal-bipyramid geometry is observed for all the peroxo complexes examined.[2b] On the other hand, direct information of the situation in solution is lacking. Moreover the ^{17}O chemical shift might be a more sensitive measure than the bond length. Therefore we have collected the ^{17}O NMR data presented in Table I.[19]

Control experiments by ^1H or ^{13}C NMR spectroscopy have confirmed[1,2,11] that under the experimental conditions adopted the ligands remain coordinated to the metal center.

(1) Metal Catalysis in Oxidation by Peroxides. 29. Part 28: Bortolini, O.; Campestrini, S.; Di Furia, F.; Modena, G.; Valle, G. *J. Org. Chem.* **1987**, *52*, 5467–5469.
(2) (a) Di Furia, F.; Modena, G. *Pure Appl. Chem.* **1982**, *54*, 1853–1866. (b) Di Furia, F.; Modena, G. *Rev. Chem. Intermed.* **1985**, *6*, 51–76.
(3) Sheldon, R. A.; Kochi, J. K. *Metal Catalyzed Oxidation of Organic Compounds*; Academic: New York, 1981; pp 71–119.
(4) (a) Mimoun, H.; Seree De Roch, I.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, *5*, 1481–1492. (b) Mimoun, H.; Seree De Roch, I.; Sajus, L. *Tetrahedron* **1970**, *26*, 37–50.
(5) Jacobson, S. E.; Tang, R.; Mares, F. *Inorg. Chem.* **1978**, *17*, 3055–3063.
(6) Klemperer, W. G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 246–254.
(7) Miller, K. F.; Wentworth, R. A. D. *Inorg. Chem.* **1979**, *18*, 984–988.
(8) Postel, M.; Brevard, C.; Arzoumanian, H.; Riess, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 4922–4926.
(9) Curci, R.; Fusco, G.; Sciacovelli, O.; Troisi, L. *J. Mol. Catal.* **1985**, *32*, 251–257.
(10) Gerothanassis, I. P.; Momenteau, M. *J. Am. Chem. Soc.* **1987**, *109*, 6944–6947.
(11) Di Furia, F. Abstracts of the International Symposium on *Activation of Dioxygen and Homogeneous Catalytic Oxidations*; Tsukuba, Japan, July 1987.
(12) Campestrini, S.; Di Furia, F.; Modena, G., unpublished results.
(13) Di Furia, F.; Modena, G.; Curci, R.; Bachofer, S. J.; Edwards, J. O.; Pomerantz, M. *J. Mol. Catal.* **1982**, *14*, 219–229.
(14) Bortolini, O.; Bragante, L.; Di Furia, F.; Modena, G. *Can. J. Chem.* **1986**, *64*, 1189–1195.
(15) Bortolini, O.; Campestrini, S.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1987**, *52*, 5093–5095.
(16) Le Carpentier, J. M.; Schlupp, R.; Weiss, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1972**, *B28*, 1278–1288.
(17) Westland, A. D.; Haque, F.; Bouchard, J. M. *Inorg. Chem.* **1980**, *19*, 2255–2261.
(18) Mimoun, H. *Rev. Inst. Fr. Pet.* **1978**, *33*, 259–310.
(19) Incidentally, these results appear to be somehow in contrast with previous data,[8] which indicated a significant variation of the ^{17}O chemical shift of the Mo=O group with the nature of the ligand. Such a discrepancy could be rationalized if the literature data[8] refer to protic solvent where solvolysis of the ligands and acid–base equilibria of the complexes may occur.

0022-3263/88/1953-4581$01.50/0